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Garlic Powder, Effect on Plasma Lipids, Postprandial Lipemia, Low-Density Lipoprotein Particle Size, High-Density Lipoprotein Subclass Distribution and Lipoprotein(a)

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OBJECTIVES To test the hypothesis that a garlic supplement alters plasma lipoproteins, postprandial lipemia, low-density lipoprotein (LDL) size and high-density lipoprotein (HDL) subclass distribution differently in 50 moderately hypercholesterolemic subjects classified as LDL subclass pattern A or B.

BACKGROUND Garlic has been variably reported to reduce or not affect plasma cholesterol values. Low-density lipoprotein pattern B is a common inherited disorder of lipoprotein metabolism that has been shown to have a significantly greater response to several lipid lowering treatments including low fat diet when compared with LDL pattern A individuals.

METHODS A double blind, randomized, placebo controlled trial in an outpatient lipid research clinic was performed and included fifty moderately hypercholesterolemic subjects (mean LDL cholesterol = 166 ± 22 mg/dl) classified as LDL subclass pattern A (predominantly large LDL, n = 22) or B (predominantly small LDL, n = 28). Following a two-month stabilization period, subjects were randomly assigned to a placebo or 300 mg three times a day of a standardized garlic tablet for three months.

RESULTS For all subjects, LDL pattern A and B subjects combined, garlic treatment for three months resulted in no significant change in total cholesterol, LDL cholesterol, HDL cholesterol, HDL subclass distribution, postprandial triglycerides, apolipoprotein B, lipoprotein (a) (Lp[a]), LDL peak particle diameter or LDL subclass distribution. There was no significant difference in response for the same parameters among subjects classified as LDL pattern A or B with the exception of significantly greater ($p = 0.01$) reduction in mean peak particle diameter in pattern A subjects treated with either garlic or placebo. There was no significant change in LDL subclass distribution.

CONCLUSIONS This investigation confirms that garlic therapy has no effect on major plasma lipoproteins and further, that it has no impact on HDL subclasses, Lp(a), apolipoprotein B, postprandial triglycerides or LDL subclass distribution. Garlic may have a greater effect on LDL particle diameter in LDL pattern A compared with pattern B subjects. This difference was not reflected in other plasma lipid measurements. (J Am Coll Cardiol 2000;35:321–6) © 2000 by the American College of Cardiology

Garlic (allium sativum) has been reported to have a beneficial effect on several cardiovascular risk parameters including plasma lipoproteins and postprandial lipemia (1–4). However, a recent double-blind, randomized, placebo controlled trial has reported no effect of a garlic oil preparation on serum lipoprotein values (5). Low-density lipoprotein (LDL) subclass pattern B, compared with pattern A, is an atherogenic lipoprotein profile that increases cardiovascular risk three-fold and is associated with an abundance of small LDL, moderately reduced high-density lipoprotein cholesterol (HDLC), moderately elevated triglycerides and increased postprandial lipemia (6,7). Cholesterol lowering therapies, including diet, niacin, bile acid binding resins, gemfibrozil and hormone replacement therapy, but not HMGCoA reductase inhibitor therapy, have been reported

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Abbreviations and Acronyms

Apo = apolipoprotein
BMI = body mass index
C = cholesterol
HDL = high-density lipoprotein
HDLC = high-density lipoprotein cholesterol
LDL = low-density lipoprotein
LDLC = low-density lipoprotein cholesterol
Lp(a) = lipoprotein (a)
t.i.d. = times a day
VLDL = very-low-density lipoprotein

to have a significantly different effect in patients classified as LDL pattern A versus B (8–11). Part of the confusion surrounding the effect of garlic on lipoprotein values may be due to a differential lipoprotein response in LDL pattern A versus B subjects so that the poorly responsive group blunts the effect in the entire group and masks a significant change in the responsive group. This issue is of clinical importance because, in four coronary arteriographic regression trials, LDL subclass distribution has been reported to be associated with arteriographic change following treatment (12–15).

In order to determine if garlic had a differential effect on lipoprotein response, similar to the effect of low fat diet, niacin, bile acid binding resins, gemfibrozil and hormone replacement therapy on LDL particle size, LDL subclass distribution and HDL subclass distribution, we investigated the effect of standardized garlic tablets on 50 subjects in a double blind, randomized, placebo controlled trial, with determination of LDL and HDL subclass pattern and distribution. Other measures of lipoprotein metabolism, including lipoprotein(a) (Lp[a]), apolipoprotein B (Apo B) and postprandial triglyceride response were measured in order to determine if garlic therapy impacts these parameters which may not be apparent from measures of routine plasma lipids.

METHODS

Subjects. Fifty subjects (mean age 53 ± 10 years, weight 163 ± 30 lbs) were recruited on the basis of low-density lipoprotein cholesterol (LDLC) >150 mg/dl and <200 mg/dl and triglycerides <300 mg/dl. Informed consent was obtained from all participants. Subjects were excluded if they were shown to have heterozygous familial hypercholesterolemia, a systemic illness that could affect blood lipids, body weight greater than 30% ideal, use of lipid lowering drugs in the preceding two months or other medications known to alter blood lipids. Following this phase, subjects were randomized in a double-blind manner, to placebo or garlic, 300 mg three times a day (t.i.d.) Kwai garlic tablets (Lichtwer Pharma, Pittsburgh, Pennsylvania) for 12 weeks. This dose has previously been reported to result in a significant 8% reduction in LDLC (16).

Diet analysis. All subjects were stabilized on an American Heart Association Step I diet for at least two weeks before entry into the protocol. Three-day diet records were obtained at baseline before randomization and at 12 weeks in the double blind phase. Food records were analyzed using Nutritionist III software (17).

Postprandial load. Each subject was fed a laboratory prepared 50% fat meal matched to body surface area as previously described (18).

Laboratory. Blood samples were obtained following a 16 h fast and advice to avoid alcohol for the 48 h before the blood draw. Triglyceride, total cholesterol, LDLC and HDLC were determined by enzymatic methods and a modified heparin-2M MnCl2 procedure to precipitate very-low-density lipoproteins (VLDL) and LDL (19). These measurements were monitored in the Centers for Disease Control-National Heart Lung and Blood Institute Lipoprotein Standardization Program (20). The apo B assay was carried out by a competitive enzyme-linked immunoassay procedure using well-characterized and specific monoclonal antibodies (21). Lipoprotein(a) concentration was measured with an enzyme-linked immunosorbent assay kit [Macra Lp(a) Terumo Diagnostics Division] as described previously (22). This assay uses a monoclonal capture antibody immunospecific to Apo (a) and a peroxidase-conjugated polyclonal detection antibody with recognition of the entire Lp(a) molecule. Internal quality assurance for apolipoproteins was monitored at two levels for each analyte on an ongoing basis using specifically prepared frozen pools. Apolipoprotein E isoforms were determined by isoelectric focusing of VLDL aoplipoproteins and phenotypes designated according to recommended nomenclature (23,24). Throughout the period in which all apolipoprotein measurements were performed, the laboratory participated in the CDC-IUIS Apolipoprotein standardization program (25).

Identification and densitometric measurements of LDL species were carried out using Pharmacia PAA 2/16% gradient gels as described previously (26,27). Criteria described previously (28) were used to classify the LDL subclass pattern as either pattern A, which had the predominant peak >262 angstrom with skewing to the right, or pattern B, which had the predominant peak <255 angstrom with skewing to the left. In the size range between 255 and 262 angstroms (15% to 20% of subjects), peaks can be symmetric, broad or multimodal and result in an intermediate LDL subclass pattern. For purposes of analysis, subjects classified as the intermediate pattern were included in the LDL pattern B group. Percent LDL distribution in seven regions (I, IIa, IIb, IIIa, IIIb, IVa, IVb) was determined. Region IIIa + IIIb correlates with the atherogenic region (Sf3–5) on analytic ultracentrifugation.

High-density lipoprotein subclass distribution was determined by gradient gel electrophoresis of HDL and was performed as previously described (28). Electrophoretic

Table 1. Baseline Mean Group Variables

	All Subjects (n = 50)	Garlic (n = 25)	Placebo (n = 25)	p
Triglyceride	137 ± 59	145 ± 54	128 ± 63	0.31
TG pp	304 ± 146	320 ± 135	287 ± 156	0.43
TC	245 ± 26	250 ± 29	239 ± 23	0.17
LDLC	166 ± 22	169 ± 25	162 ± 18	0.24
HDLC	51.6 ± 12.1	51.3 ± 11.5	51.9 ± 12.8	0.86
LDL dia (A)	256.1 ± 9.2	255.8 ± 9.2	256.4 ± 9.3	0.80
LDL IIIa + IIIb%	19.6 ± 10.3	20.2 ± 10.7	19.0 ± 10.1	0.69
HDL2b%	16.5 ± 7.3	14.8 ± 7.1	18.2 ± 7.2	0.10
HDL2a%	23.0 ± 4.7	22.9 ± 3.9	24.0 ± 5.3	0.14
HDL3a%	35.4 ± 6.0	37.7 ± 5.5	33.2 ± 5.7	0.006
HDL3b%	18.2 ± 5.8	19.3 ± 6.1	17.1 ± 5.3	0.18
HDL3c%	6.7 ± 5.6	6.1 ± 3.6	7.4 ± 5.0	0.29
Apo B	126 ± 27	125 ± 23	127 ± 32	0.75
Lp(a)	27.6 ± 28.5	28.8 ± 33.5	26.3 ± 22.9	0.76

Mean (±SD) baseline triglyceride (mg/dl), lipoprotein cholesterol (mg/dl), LDL peak particle diameter (Angstom), apolipoprotein B (mg/dl) and percent distribution in HDL2b, HDL2a, HDL3a, HDL3b and HDL3c values. LDLC = low density lipoprotein cholesterol; HDLC = high density lipoprotein cholesterol; Apo = apolipoprotein.
TG pp = triglycerides 4 h after standard oral fat load.

bands representing the HDL subspecies HDL-2b, HDL-2a, HDL-3a, HDL-3b and HDL-3c are identified and densitometrically scanned using a computer assisted scanning procedure developed at the Donner Laboratory, University of California, Berkeley. The HDL region is by definition, a density (d) less than 1.21 g/ml, which is then stained following GGE.

Statistics. Statistical analysis involved a Student *t* test to test for significance of difference between groups and change from baseline values within groups. Analysis of variance was used to test for the significance of difference in response between groups. Statistical tests were performed using Statview software (29).

RESULTS

At randomization, there were no significant differences between treatment groups for lipid measurements including triglycerides, postprandial triglyceride response, total cholesterol, LDL cholesterol, LDL peak particle diameter, LDL subclass distribution, HDLC, apo B, and Lp(a) (Table 1). There was no significant difference in body mass index (BMI), blood pressure or diet variables including total calories, percent calories from total fat, saturated fat, carbohydrate, alcohol, grams of cholesterol or grams of soluble and insoluble fiber. At baseline, there was no significant difference between the group randomized to garlic or placebo for any of the lipoprotein measurements, BMI or diet analysis with the exception of a significantly higher HDL3a% distribution ($p < 0.01$) in the garlic compared with placebo group (Table 1). At baseline, previously described differences between LDL pattern A (n = 28) and B (n = 22) subjects, were observed. Specifically, fasting triglycerides (112 ± 50 mg/dl pattern A, 169 ± 54 mg/dl pattern B) and postprandial triglyceride change (96 ± 59 mg/dl pattern A, 173 ± 85 mg/dl pattern B) were significantly higher ($p < 0.001$), HDLC (55.8 ± 12.7 mg/dl pattern A, 46.3 ± 8.9 mg/dl pattern B) significantly lower ($p < 0.005$), LDL peak particle diameter (268 ± 6A pattern A, 255 ± 6A pattern B) significantly smaller ($p < 0.0001$) and percent distribution in LDL IIIa + IIIb (12.2 + 3.5% pattern A, 28.8 + 8.4% pattern B) significantly higher ($p < 0.0001$) in the LDL subclass pattern B subjects compared with pattern A (3). In pattern B subjects, percent distribution in HDL2b was significantly lower ($p < 0.01$) and distribution in HDL3b significantly higher ($p < 0.01$) than pattern A subjects. Body mass index (24.5 ± 3.9 pattern A, 26.6 ± 4.3 pattern B) was higher ($p = 0.07$) in pattern B subjects.

In the 50 participants, 12 had an Apo E 4/3 phenotype (5 garlic, 7 placebo), one an Apo E 3/2 phenotype (placebo) and one an Apo E 4/2 phenotype (placebo). The remaining 36 participants had Apo E 3/3 phenotype.

There was no significant effect of therapy on change in levels of fasting triglycerides, postprandial triglycerides, total cholesterol, LDL cholesterol, LDL peak particle diameter, LDL subclass distribution, HDL cholesterol, HDL subclass distribution, Apo B or Lp(a) (Table 2). There was no significant between-group differences for change in BMI, systolic or diastolic blood pressure or diet variables between the garlic versus placebo group.

Within the pattern A and pattern B groups, comparison of garlic versus placebo treatment differences revealed no significant differences for change in fasting triglycerides, postprandial triglycerides, LDL cholesterol, LDL subclass distribution, HDL cholesterol, Lp(a), Apo B, postprandial

Table 2. Mean Change Values (mg/dl, ±SD) for All Subjects Randomized to the Placebo or Garlic Group

	Garlic (n = 25)	Placebo (n = 25)	p
Triglycerides	−4.3 ± 43.8	21.5 ± 96.8	0.23
TG pp	−49.6 ± 73.6	−24.8 ± 87.1	0.28
Total cholesterol	−2.5 ± 26.4	1.2 ± 19.0	0.57
LDL cholesterol	−1.7 ± 25.5	−3.2 ± 14.9	0.80
HDL cholesterol	−0.1 ± 6.6	0.2 ± 8.9	0.91
LDL diameter (A)	−1.7 ± 7.8	−3.7 ± 7.0	0.35
LDL IIIa + b%	3.9 ± 15.0	4.3 ± 10.8	0.91
Apo B	−0.7 ± 25.3	−7.0 ± 31.8	0.45
Lp(a)	−2.5 ± 15.4	−0.7 ± 8.2	0.61
HDL2a%	0.4 ± 4.5	0.8 ± 5.6	0.76
HDL2b%	1.0 ± 4.1	−0.6 ± 7.9	0.36
HDL3a%	−1.8 ± 6.1	1.2 ± 7.7	0.13
HDL3b%	−0.2 ± 4.5	−0.6 ± 7.1	0.78
HDL3c%	0.6 ± 6.2	−0.7 ± 8.0	0.52

Low density lipoprotein diameter (A) in angstroms. p is the significance of the difference between the change in the placebo group compared with the garlic group.

Apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); TG = triglyceride.

triglycerides, HDL subclass, as well as diet records, systolic or diastolic blood pressure or BMI. The only significant difference (p = 0.01) was a greater reduction in LDL peak particle diameter in pattern A subjects in both the garlic and placebo groups, compared with pattern B subjects (Table 3). There was no difference in the percent distribution in the seven LDL regions. There was no significant difference between the pattern A subjects treated with placebo versus garlic (p = 0.92). Comparison of change in the LDL pattern A and B groups treated with garlic revealed no significant differences with the exception of significantly greater (p = 0.02) LDL peak particle diameter in pattern B compared with A subjects. Regression to the mean is unlikely since within the placebo group there was no significant differences in diet, weight or lipoprotein variables between LDL pattern A and B subjects.

DISCUSSION

New findings. This double blind, placebo controlled trial in 50 subjects found that daily garlic supplementation had no significant effect on plasma lipids, LDL peak particle diameter, LDL subclass distribution, HDL subclass distribution, Apo B, Lp(a), postprandial lipemia and systolic and

Table 3. Mean Change (mg/dl) by LDL Pattern After Placebo or Garlic Treatment

	Pattern A		Pattern B		
	Garlic (n = 12)	Placebo (n = 16)	Garlic (n = 13)	Placebo (n = 9)	p ANOVA
Triglycerides	−12.4 ± 44.6	41.9 ± 109.6	3.2 ± 43.3	−14.8 ± 57.2	0.17
TG pp	−40.5 ± 68.5	−25.2 ± 83.6	−58.0 ± 79.8	−24.1 ± 98.3	0.70
Total cholesterol	−2.3 ± 30.8	1.3 ± 17.0	−2.8 ± 22.9	1.0 ± 23.3	0.96
LDL cholesterol	1.1 ± 30.2	−6.0 ± 15.0	−4.3 ± 21.3	3.3 ± 21.3	0.61
HDL cholesterol	−1.0 ± 8.3	−0.1 ± 9.3	0.8 ± 4.7	0.7 ± 8.6	0.94
LDL diameter (A)	−5.4 ± 7.0	−5.7 ± 6.8	1.7 ± 7.1	−0.1 ± 6.0	0.01
LDL IIIa + b%	10.4 ± 4.2	5.5 ± 10.4	−1.6 ± 14.2	2.3 ± 11.8	0.14
Apo B	3.3 ± 31.2	−5.1 ± 19.8	−4.4 ± 19.0	−10.8 ± 49.6	0.75
Lp(a)	3.1 ± 11.0	−1.4 ± 9.0	−7.7 ± 17.3	0.6 ± 6.6	0.16
HDL2a%	0.2 ± 3.6	1.5 ± 4.5	0.5 ± 5.4	−0.4 ± 7.2	0.81
HDL2b%	0.5 ± 4.0	0.3 ± 7.3	1.5 ± 4.4	−2.2 ± 9.0	0.60
HDL3a%	−1.2 ± 5.4	−0.4 ± 7.9	−2.5 ± 6.8	4.0 ± 7.0	0.19
HDL3b%	0.7 ± 3.6	−1.8 ± 4.6	−0.9 ± 5.2	1.3 ± 10.2	0.56
HDL3c%	0.1 ± 3.5	0.4 ± 8.7	1.1 ± 8.0	−2.6 ± 6.8	0.68

Apo = apolipoprotein; HDL = high density lipoprotein; LDL = low density lipoprotein; Lp(a) = lipoprotein; TG pp = triglycerides postprandial.
LDL diameter in angstroms.

diastolic blood pressure. The only significant finding was a greater reduction in LDL peak particle diameter in the pattern A garlic and placebo groups compared with the pattern B group. This difference in LDL peak particle diameter was not paralleled by significant change in triglycerides or HDLC which is often reported with LDL peak particle diameter change. In addition, there was no difference in the LDL percent distribution in the seven LDL subclass regions. In particular, there was no significant difference between placebo and treatment for postprandial triglyceride concentration. Elevated fasting triglycerides (>160 mg/dl) and low HDLC (<35 mg/dl) are often, but not always, associated with LDL pattern B. In this investigation, 48% of LDL pattern B subjects had a fasting triglyceride <160 mg/dl and only 11% had a HDLC ≤35 mg/dl. Forty-four percent of LDL pattern B subjects would have been mistakenly classified if fasting triglycerides >160 mg/dl or HDLC ≤35 mg/dl were used as surrogate markers of LDL subclass pattern B.

Previous garlic studies. It is important that no diet composition or BMI changes were documented in this investigation since changes in these parameters could have affected lipoprotein values independently of any garlic effect. A previous garlic study in 42 subjects reported an 8% LDLC reduction in response to 900 mg/d for 12 weeks compared with placebo, which was statistically significant ($p < 0.05$) (17). A second investigation in 41 subjects reported a significant reduction (7%) in total plasma cholesterol attributed to an aged garlic extract (4). However, in both studies, subjects were either questioned as to any changes in diet or advised to adhere to a National Cholesterol Education Program Step I diet. There was no report of quantitative diet record assessment. Thus, it is unclear if diet change could have accounted for part of the observed LDLC lowering result in the garlic group. The reports using metaanalysis to assess the effect of garlic on lipoproteins do not include diet records as a criteria for inclusion in their analysis. A recent investigation of a garlic oil preparation used seven-day diet records to assess nutritional status and found no change in total cholesterol, LDLC, HDLC or triglycerides in 25 subjects in a randomized, placebo controlled design in which it was documented that no diet composition change occurred (5). The lack of LDLC change in this recent study and the study reported here may be due to inadequate sample size although this is unlikely since the previous studies with 42 and 41 subjects reported a significant reduction in total cholesterol and LDL cholesterol (4,17).

Apo E isoforms. Another potential confounding variable in LDLC response to diet change is Apo E isoform differences. Individuals with an E4 allele have a significantly greater reduction in LDLC than individuals with the Apo E 3/3 isoform in response to a reduced fat diet and differences in the prevalence of the E4 allele in the treatment and placebo groups may confound data interpretation (30). In our investigation the E4 allele was almost equally distributed, five in the garlic group and seven in the placebo group. It is unlikely that diet response differences due to Apo E isoform differences contributed to any bias in our investigation.

Postprandial lipemia. In our investigation, both the placebo and treatment group showed reduced postprandial triglycerides at the second test. Following garlic treatment, the postload triglycerides decreased 49.6 ± 73.6 mg/dl in the garlic group. When the postprandial triglyceride reduction was compared within the garlic group for treatment effect versus baseline, a significant difference ($p < 0.003$) was found, but when compared with the 24.8 ± 87.1 mg/dl reduction in the placebo group, the postprandial triglyceride reduction in the garlic group lost its statistical significance ($p = 0.28$). Improvement in postprandial lipemia has been reported in a study group of 24, but the change was not statistically significant compared with the control group (2).

Conclusion. A recent randomized trial has reported no effect of garlic oil on lipoprotein cholesterol levels (31). The double blind, randomized clinical trial we report confirms this lack of effect of garlic on routine measures of triglycerides, total, LDL and HDL cholesterol. However, it contributes new information to the field by further revealing no significant effect of 300 mg t.i.d. of KWAI garlic on LDL peak particle diameter, LDL subclass distribution, Apo B, Lp(a), HDL subclass distribution and postprandial lipemia. Our study controlled for potential variables including diet composition, BMI and Apo E isoforms. There was a significantly greater reduction in LDL peak particle diameter in LDL pattern A subjects who received either garlic or placebo compared with LDL pattern B subjects treated, and the implications of this are unclear.

This issue is clinically relevant since lipid lowering treatments such as low fat diet, nicotinic acid, gemfibrozil and hormone replacement therapy have been shown to have an effect on either lipoprotein subclass distribution, Lp(a) or postprandial lipemia that is not apparent from routine measures of triglycerides, total, LDL or HDL cholesterol (7–11,32). For example, change from a 46% fat diet to a 24% fat diet resulted in a 10% reduction in LDLC in LDL pattern A men and 20% in LDL pattern B men ($p < 0.02$) (8). No such differential response was documented with garlic in this investigation. Differences in LDL subclass pattern and response to treatments are important in predicting CAD risk and in selecting the most appropriate treatment (7). Potential antiatherogenic mechanisms not tested in this trial may contribute to an, as yet, unclear role for garlic in the atherosclerosis armamentarium (33–35).

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